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Pleomorphic Adenoma of the Minor Salivary Glands: a Case Report and a Review of the Literature

Case Report

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Resumo

Os tumores das glândulas salivares são raros e constituem cerca de 3 a 6% de todos os tumores da cabeça e do pescoço. O adenoma pleomórfico, também conhecido por tumor misto, é uma neoplasia benigna e é o tumor mais comum das glândulas salivares. Este afecta maioritariamente as glândulas salivares major, mais especificamente a glândula parótida, e menos frequentemente as glândulas salivares minor. O palato é o local mais comum para a origem do tumor misto das glândulas salivares minor. Quanto mais pequena for a glândula salivar afectada, maior é a probabilidade de se malignizar. O seu pico de incidência ocorre entre os 40 e os 50 anos e é ligeiramente mais frequente no sexo feminino. Este tumor tem sido associado a alterações do cariótipo em cerca de 70% dos casos. É descrito um caso clínico de um adenoma pleomórfico das glândulas salivares minor do palato mole, numa doente de 20 anos e do sexo feminino, que já apresentava um diâmetro crânio-caudal de 5 cm.
Palavras-chave: Adenoma pleomórfico; tumor benigno; glândulas salivares minor; palato mole; excisão.

Abstract

Salivary gland tumors are rare and account for 3 to 6% of tumors occurring in the head and neck. Pleomorphic adenoma, also known as mixed tumor, is a benign neoplasm and it is the most common salivary gland tumor. It affects mostly the parotid gland and other major salivary glands, and less frequently the minor salivary glands. The palate is the most common site for mixed tumors of the minor salivary glands. The smaller the salivary gland that is affected, the more likely it is to trigger a malignant tumor. The incidence peak of pleomorphic adenoma is between 40 to 50 years of age and it is slightly more frequent in females. This tumor has been associated with abnormal karyotypes in up to 70% of cases. A case of a pleomorphic adenoma of the minor salivary glands of the soft palate in a 20 year-old female patient which had already 5 cm of cranio-caudal diameter is described.
Key words: Pleomorphic adenoma; benign tumor; minor salivary glands; soft palate; excision.

INTRODUCTION

The salivary glands are divided into major and minor salivary gland categories. The major salivary glands are the parotid, the submandibular, and the sublingual glands. The minor glands are dispersed throughout the upper aerodigestive submucosa.

Salivary gland neoplasms are uncommon and account for 3 to 6% of all head and neck tumors.[1-4] They exhibit a wide range of benign and malignant histologic types. Most salivary gland tumors (SGTs) originate, by far, in the parotid gland (80%) [5,6], followed by the minor salivary glands (22%), submandibular (8%) and sublingual (1%) glands.[1-3,7] Most SGTs are benign, nevertheless 25% of parotid tumors, 45% of submandibular tumors, 80% of sublingual tumors and 75% of minor salivary gland tumors are malignant.[1,5,6]

The most common malignant tumors are mucoepidermoid carcinoma, adenoid cystic carcinoma and polymorphous low-grade adenocarcinoma.

The etiology of SGTs is so far unknown. Putative risk factors include cigarette smoking, viral infections, rubber manufacturing workers, genes etc. The only well-established risk factor is ionizing radiation.[3,5,8,9] Genetic alterations, such as allelic loss, monosomy and polysomy, and structural rearrangement, have all been studied as factors in the development of these tumors.[9-12]

Pleomorphic adenoma (PA) is the most common benign tumor of the salivary glands, accounting for about 70% of all the salivary gland tumors.[9,13,14] It affects mostly the parotid gland and other major salivary glands, less frequently the accessory glands. The majority of the minor gland PAs occur in the palate (55%) followed by the lip (25%), and a small minority are located in the buccal mucosa, floor of the mouth, tongue, pharynx, retromolar area, gingiva and nasal cavity.[13,15-17] Although PAs are classified as benign, they are frequently multinodular and may recur, can undergo malignant transformation and can even metastasize.[8,11,14] The incidence peak of PA is between 40 to 50 years old and studies revealed that is slightly more frequent in females.[15,18,19] Clinically a PA in the soft palate presents as a painless swelling without ulceration or surrounding inflammation.

The diagnosis of PA is established on the basis of history, physical examination, cytology and histopathology. Computed tomography (CT) scan and magnetic resonance imaging (MRI) provide information of the localization, size, extension of tumor to the surrounding superficial and deep structures.

The gold standard treatment for PA in minor salivary glands is wide local excision with removal of periosteum and involved bone. Simple enucleation of this tumor leads to high local recurrence rates and should be avoided. [13,17]

CASE REPORT

A 20-year-old female patient reported to the Department of Head and Neck Surgery with the chief complaint of a painless swelling on the left soft palate (arrow) for the past 6 months with a deviation of the uvula (asterisk) (Fig. 1).

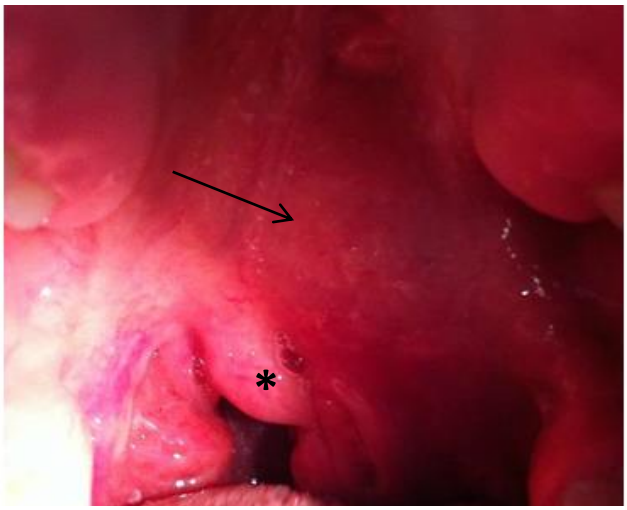

Fig.1. Intraoral examination. Swelling on the left soft palate (arrow) with deviation of the uvula (asterisk).

Swelling was insidious in onset and gradually increasing in size. The deviation of the uvula was what the patient first noticed. There was no preceding history of trauma and no relevant past medical history. Intraoral examination (Fig.2) revealed a solitary, oval-shaped, red-colored, circumscribed lesion on the left soft palate (arrow), crossing the midline and pushing the uvula to the right (asterisk), measuring approx. 3 x 2 cm. On palpation, swelling was soft in consistency with well-defined borders, non-tender, non-fluctuant, non-reducible and non-mobile. The overlying mucosa was smooth and intact. The submandibular lymph nodes on the left side were enlarged, painless and movable. Her general physical and systemic examination was normal.

Clinical differential diagnoses of lipoma, benign tumors, such as the pleomorphic adenoma were considered, as well as malignant tumors, such as the mucoepidermoid carcinoma, adenoid cystic carcinoma and the polymorphous low-grade adenocarcinoma.

Contrast-enhanced computed tomography (Fig. 3) revealed a well-circumscribed hypodense mass, situated in the soft palate on the left side, measuring approximately 46 x 32 mm in the transverse plane with a cranio-caudal diameter of 51 mm. The mass was somewhat heterogeneous with an extensive cystic/necrotic constitution. It developed through the parapharyngeal space and extended into the left carotid space and it was invading the jaw muscles, namely the medial pterygoid. The mass was also growing for the naso and oropharynx, pushing the airway slightly to the right. Fine-needle aspiration (FNA) cytology showed morphology compatible with a primitive epithelial-myoepithelial salivary gland tumor, with chondromyxoid fibrillary stroma, suggestive of a pleomorphic adenoma. A wide excision of the lesion was performed along with curettage of underlying bone, under general anesthesia. The whole tumor mass was separated out with careful dissection of the carotid space. The specimen was sent for histopathological examination (Figs. 4a, 4b, 4c, 4d). Macroscopic description showed a surgical specimen of tumorectomy with 34 g and 50 x 40 x 20 mm, consisting of a capsulated nodular tumor, whose surface section is pearly and

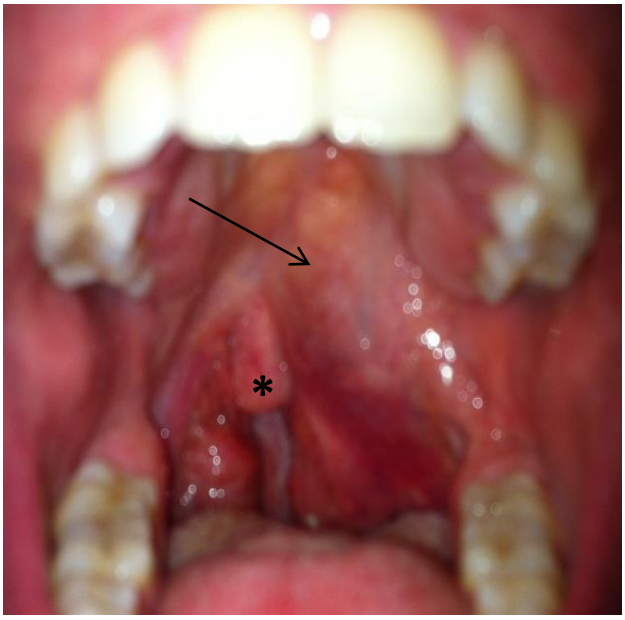

Fig..2. Intraoral examination revealing a solitary, oval-shaped, red-colored, circumscribed lesion on the left soft palate (arrow), crossing the midline and pushing the uvula to the right (asterisk).

Fig..3. Contrast-enhanced computed tomography revealing a well-circumscribed hypodense mass, situated on the left soft palate (asterisk).

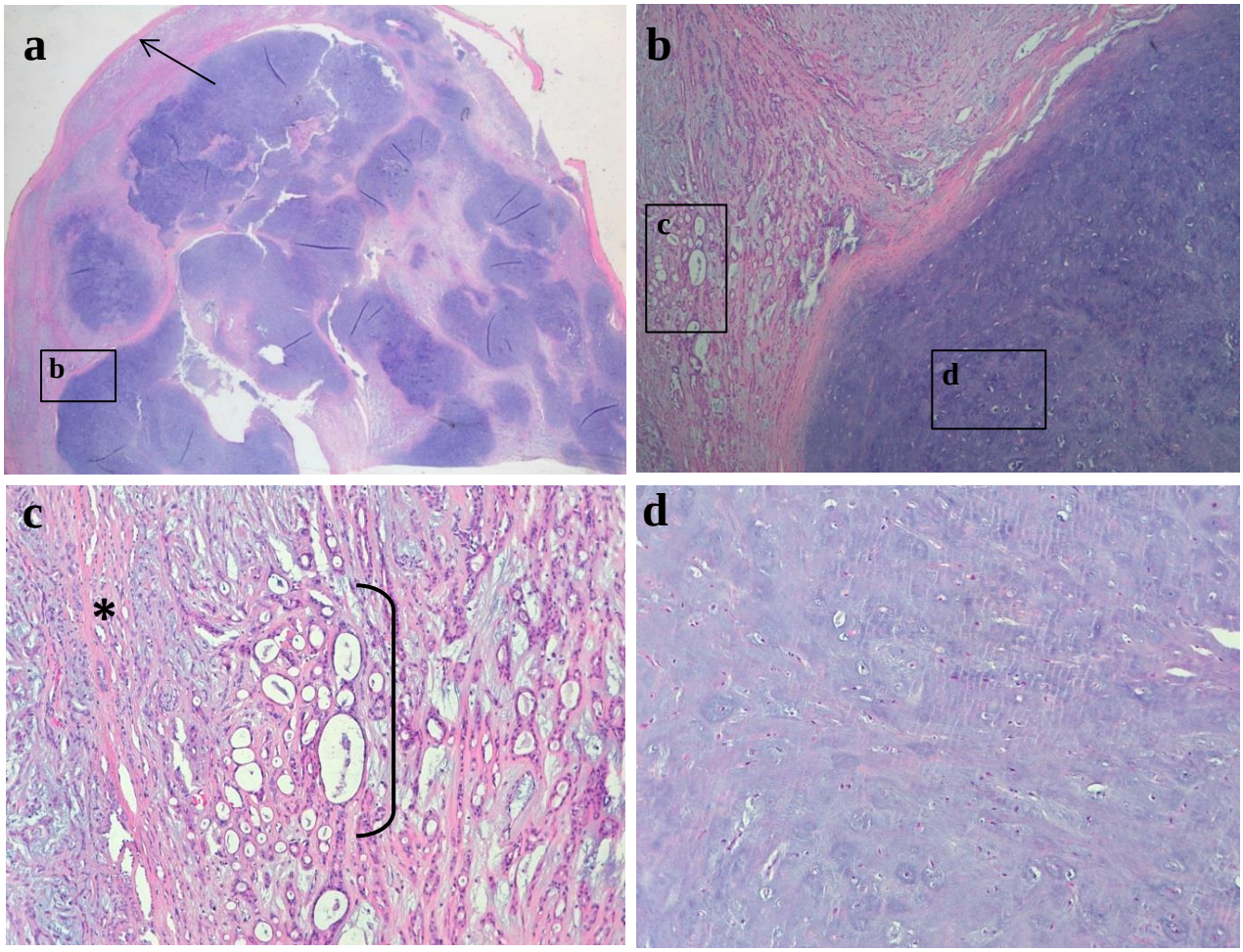

Fig..4. Pleomorphic adenoma. Histology showed an en capsulated (arrow) multinodular tumor (Fig. 4a) with a tubular and ductular pattern (parentheses) in a myxoid stroma (asterisk) (Fig. 4b, 4c) and a chondromyxoid stroma (Fig. 4b, 4d).

elastic, with myxoid areas. Histology showed an encapsulated multinodular tumor (Fig. 4a) with a tubular and ductular pattern in a myxoid stroma (Fig. 4b, 4c) and with a chondromyxoid stroma (Fig. 4b, 4d).

Fig. 5. Postoperative.

The result was in agreement with the specimen taken before the surgery and confirmed the diagnosis of pleomorphic adenoma. The entire lesion was excised, with juxta-lesional margins.

There were no postoperative (Fig. 5) complications, and no recurrence was seen during the 3 years follow-up period. The patient is still under regular follow-ups.

DISCUSSION

We report the case of a patient with PA who was successfully treated to full recovery. In spite of the clinically satisfactory outcome,

several fundamental questions concerning this particular adenoma are still open.

Macroscopy. PA tend to form well-defined, ovoid or round tumors. They are often encapsulated but the capsule varies in thickness and may be partially or completely absent, particularly in predominantly mucoid tumors. Those PAs developing in the minor glands usually have a poorly developed or absent capsule. The outer surface of larger tumors is frequently bossellated. The cut surface is typically homogeneous and white or tan. It may have a glistening appearance where there are cartilaginous or myxochondroid areas.[22]

Histology. Histologically, PAs contain groups of epithelial and myoepithelial cells in varying stages of organization. The proportion of each of these elements varies widely and one or the other is often predominant.[13] The essential components are the capsule, epithelial and myoepithelial cells, and mesenchymal or stromal elements. The epithelium usually forms sheets or duct-like structures. The ducts show cuboidal luminal cells and there may be an abluminal layer of myoepithelial cells. The mesenchymal-like component is mucoid/ myxoid, cartilaginous or hyalinized and sometimes this tissue forms the bulk of the tumor. The cartilage-like material appears to be true cartilage and is positive for type II collagen and keratin sulphate.[22] Some long-standing tumors show increasing hyalinization and the epithelial component is progressively effaced. Bone may form within this cartilage or form by osseous metaplasia of the stroma. The myoepithelial cells frequently separate from the epithelial nests and give rise to a chondromyxoid or hyalinized stroma. Thus, the demarcation between epithelial nests and stromal cells may be indistinct, as myoepithelial cells appear to drop off from the epithelial nests.[23] The presence of chondromyxoid matrix material is the most specific feature for making the correct diagnosis.[16] Most tumors show areas where finger-like processes extend into the capsule.

Histogenesis. The histogenesis process of PA of salivary gland continues to remain a controversial subject. While some authors suggest the origin of the two tumoral components (parenchyma and stroma) from different sources, mesenchymal and myo(epithelial), the majority confirms and proves the unicellular origin of this tumor from the epithelial cells. [9,10,13,14,17] Enescu et al[9], demonstrated the existence of an epithelial-mesenchymal transition process in PA, using the reactivity for E-cadherin and α-SMA (alpha-smooth muscle actin) expression, showing the process through which the epithelial neoplastic cells transdifferentiate into mesenchymal cells. Satpathy et al[14] showed an important role of mucins in cancer development and invasion. Like normal epithelial tissue, cancer cells use mucins to control the environment, regulate differentiation and proliferation and enhance invasive and metastatic properties. They confirmed the role of myoepithelial cells in stromal histogenesis. The neoplastic myoepithelial cells differentiate to stellate cells, which produce the myxoid matrix, and they further differentiate into chondroblastic cells, which develop cartilaginous areas by synthetizing mucopolysaccharides. They also noted the change in mucin profile from neutral mucins to acidic mucins as the neoplasm progresses. Matsumoto et al[12], studied the mechanism behind chondrogenesis, examining the expression of transcription factors related to chondrogenesis in tumors and salivary glands. This study provided indirect but conclusive evidence that epithelial cells differentiate to chondrocytes during tumorigenesis of salivary gland PA, indicating that salivary gland cells

have potential for chondrogenesis. This model predicts that Twist1 (a member of the basic helix-loop-helix family of transcription factors) expression prevents salivary gland cells from fulfilling the chondrogenic potential, and Twist1 depletion concomitant with neoplastic transformation permits them to differentiate toward chondrocytes and produce cartilage-like mesenchymal tissues in PA.

Chromosomal alterations. PA has been associated with abnormal karyotypes in up to 70% of cases,[21, 22] with nonrandom involvement of 8q12, the locus of the pleomorphic adenoma (PLAG1) gene. However, PLAG1 has also be shown to be activated in cases of PA either with normal karyotypes or with 12q13-15 abnormalities. The PLAG1 protein is a nuclear oncoprotein that functions as a DNA-binding transcription factor. Downregulation of PLAG1 target genes, including IGF2 (insulin-like growth factor 2), is likely to play a major role in the genesis of PA. [22] The trisomy 8 is known to be the most frequent numerical deviation found in salivary gland tumors, being present in benign and malignant tumors. The mechanisms associated with gain of chromosomes are still unclear; the most plausible explanation is that gene dosage alterations predispose to tumor proliferation.[10] Previous studies have indicated that patients with karyotypically normal adenomas are significantly older than those with rearrangements of 8q12 and that adenomas with normal karyotypes are often more stroma rich than tumors with 8q12 abnormalities. [22]

Clinical course. Clinically PA presents as a slow-growing, asymptomatic, painless, unilateral firm mass with a normal overlying surface color, that may become large if is untreated. Pain, tenderness and ulceration are unusual. When originating in the minor salivary glands, in most cases it occurs in the soft and hard palate due to the highest concentration of salivary glands there and is typically a firm or rubbery submucosal mass without ulceration or surrounding ulceration.[13,20] The more common palatal mixed tumors are located laterally and rarely cross the midline.[14] Symptoms due to more advanced minor salivary gland tumors can include nasal obstruction, congestion, vision changes, or trismus when present in the nasal cavity or maxillary sinus. Minor salivary gland tumors involving the nasopharynx usually present at an advanced stage and invasion of the skull base, intracranial extension, or involvement of cranial nerves can occur.[5] In contrast, malignant lesions exhibit fast growth and adhere to deep layers, with an ulcerated or telangiectatic surface. Pain is the most suggestive characteristic of malignancy.[4]

Diagnosis by histopathology. Histopathological sampling procedures include fine needle aspiration cytology (FNAC) and core needle biopsy (bigger needle compared to FNA). FNA operated in experienced hands, can determine whether the tumor is malignant in nature with 90% sensivity. FNA can also distinguish primary salivary tumor from metastatic disease. By the fact that PA has different histological characteristics in some situations, the diagnosis of these lesions, after FNAC, can be interpreted wrongly.[19] Core needle biopsy is more invasive but it is more accurate compared to FNA with diagnostic accuracy greater than 97%.[17,24] False positive and false negative rates of FNAC range from 1 to 14%.[16]

Diagnosis by imaging methods. The role of imaging studies is to differentiate neoplastic from benign disease, define intra- versus extra-glandular location, assess local extension and invasion, and detect nodal and systemic metastases. CT with intravenous contrast is widely used to detect bone invasion, thus it is superior to MRI in evaluating bone, especially

in diagnosing erosion and perforation of the bony palate and possible involvement of the nasal cavity or maxillary sinus. MRI, with its high resolution for soft tissue, provides better definition of the vertical and inferior tumor extension through its multiplanar capacity and the tumor-muscle interface and more clearly indicates the degree of encapsulation.[17,25] MRI is suggested in evaluation of all sublingual gland tumors given the high risk for malignant disease.[5] Both can provide the extension of a SGT and anatomic details that are useful for surgical planning. Ultrasound is also frequently used to guide FNA or core needle biopsy.[24]

Staging and therapy of salivary gland tumors. Malignancies of the parotid, submandibular, and sublingual glands are staged according to the American Joint Committee on Cancer (AJCC) and the International Union for Cancer Control Tumor, Nodes, Metastasis (TNM) system. Tumors arising in minor salivary glands are staged according to their anatomic site of origin.[5]

The mainstay of the treatment for SGT is a complete surgical resection with a surrounding cuff of normal tissue. The excision should include periosteum or bone if this are included.[6,24] Every attempt should be made to ensure negative resection margins, since positive margins are associated with worse prognosis.[25] Some studies demonstrate that PA has occasionally lack of encapsulation and pseudopodia.[13] So although most PAs are encapsulated or at least circumscribed, simple enucleation of a PA is frequently associated with local recurrence. According to Debnath et al [24], if complete resection cannot be achieved, adjuvant radiotherapy should be added to improve local control. In this case, the surgical resection with a surrounding cuff of normal tissue was possible in almost all tumor's surrounding area, except the tumor's margin next to the carotid space due to its proximity. But it was possible to do a complete extraction of the capsule without disruption and no radiotherapy was advocated.

Enucleation of PA leads to a high recurrence rate, so it should be avoided. Surgical exposure of the tumor or tumor capsule risks spillage and dramatically increases the risk of recurrence, but PAs of the minor salivary glands have little propensity for recurrence (a recurrence rate of 2 to 44%, but mainly of the parotid gland).[13] Inadequate surgical procedure was reported to be the main cause of failure. The most frequent surgical issues are pseudopodia, capsular penetration, rupture of tumors and multi nodularity.

Potential for malignancy. While PA is considered pathologically and clinically benign, it can undergo malignant transformation in situ, termed *"carcinoma ex-pleomorphic adenoma*" (CaExPA), with an incidence of 2 to 7% of PAs.[8,23,24] This may be manifested by sudden growth of a previously stable mass in a salivary gland, usually the parotid. The prognosis of a carcinoma arising within a PA is largely but not entirely dependent upon the extent of invasion. Cases where the carcinoma component was confined within the tumor capsule have not recurred or metastasized, in contrast to the aggressive behavior seen with invasive CaExPA. Other prognostic factors include grade, tumor size and lymph node status. Frequent local recurrences and distant metastases mark the clinical course of invasive CaExPA. Therefore CaExPA should be considered a high-grade malignancy requiring treatment at the initial diagnosis, as subsequent salvage options are limited.[23] Ramachandran et al[11], demonstrated that WIF1 (Wnt inhibitory factor 1) downregulation is a widespread event in human salivary gland CaExPa. WIF1 downregulation occurs at a high

frequency in PAs that have progressed to CaExPa, but is rare in PAs that have not progressed to malignancy. Therefore, it was suggested that WIF1 expression could be considered in routine histopathology analysis of PA samples, as it might indicate a higher risk of progression from PA to CaExPa.

A much rarer phenomenon can also occur whereby a PA demonstrates clinically malignant behavior while remaining histologically benign, termed metastatic pleomorphic adenoma (MPA).[8,13,16,19] It can metastasize as long as 7 years[26] or even 24 years later.[8] Patients at risk of MPA have a history of recurrent or incomplete treated PA, and as no current molecular or histological parameters can predict the development of MPA, such patients should be considered for screening for metastatic disease.[8] Recurrences are rare in the minor glands and appear to be much more likely in younger patients. [22]

Hence, the long term follow up becomes imperative to evaluate possible recurrences, malignant transformation or metastases of these lesions.[16,17,19]

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